Lesson of the week

Narcolepsy mistaken for epilepsy

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Narcolepsy is common: its cardinal symptoms can give rise to confusion with epilepsy

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Narcolepsy is a distinctive but underdiagnosed disorder of sleep and waking. Its cardinal manifestations are: (*a*) excessive daytime sleepiness, with a tendency to nap repeatedly through the day; (*b*) cataplexy, a loss of muscle tone triggered by emotion, causing immobility for seconds to minutes; (*c*) hypnagogic hallucinations, vivid visual or auditory phenomena, experienced at the onset of sleep; and (*d*) sleep paralysis, an inability to move on first awakening.[1]

When a patient describes all these symptoms the diagnosis should be straightforward. Diagnostic difficulty arises when patients present with isolated symptoms, or if their story suggests some more familiar diagnosis. We report on three patients recently encountered in whom narcolepsy was initially mistaken for epilepsy. Indeed, Gelineau, the French physician who coined the term "narcolepsy" in 1880, was at pains to distinguish his novel disorder of sleep (narco from the Greek for "sleep" and "lepsy" for taken hold by) from epilepsy, with which he thought it might be confused.[2 3]

Case reports

Case 1—A 26 year old woman was found in the bath "unable to move, speak, or get out." Her husband reported flickering of the eyelids and muscle twitching. Her speech was slurred as she recovered, over minutes. The referral letter noted a history of short periods of apparent daytime sleep, sometimes at inappropriate moments—for example, during meals—and a tendency to "go weak and limp … if she is having a carry-on or laughing heartily." The diagnosis at referral was of complex partial seizures; sodium valproate had been prescribed. It emerged that she had clear recall of her period of immobility in the bath: it resembled her episodes of weakness on laughing. On direct questioning she described sleep paralysis and hypnagogic hallucinations. She tended to sleep poorly at night. The combination of daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations suggested narcolepsy. Her HLA type, determined by the microlymphocytotoxicity technique using commercially obtained antisera, was DR15[2], DQ6[1], consistent with narcolepsy. Overnight polysomnography gave normal results, but a multiple sleep latency test gave a mean sleep onset time of 4 minutes (normally more than 10), with rapid eye movement sleep in the first 15 minutes of two of her five recorded naps (normally none). These results confirmed the diagnosis. Sodium valproate was withdrawn. Clomipramine controlled her cataplexy; her daytime sleepiness has improved on treatment with stimulants.

Case 2—A 23 year old builder complained of excessive sleepiness over two years causing difficulties at work. His general practitioner was concerned by the possibility of epilepsy. Assessment in a general medical clinic elicited a story of "tonic-clonic seizures which occur during sleep," based on a description from his girlfriend. He was a loud snorer. An electroencephalogram gave a normal recording, but he became drowsy repeatedly during the procedure. We subsequently obtained a history of disabling episodes of cataplexy: he had learnt to keep a straight face to avoid laughter and the resulting weakness. He also reported sleep paralysis and hypnagogic hallucinations. The true nature of the tonic-clonic seizures during sleep eventually became clear: these were episodes of cataplexy with distal muscle twitching, occurring towards the climax of sexual intercourse. His HLA type, determined by the microlymphocytotoxicity technique, was DR15[2], Drw53, DQ1,3, consistent with narcolepsy. Overnight polysomnography suggested mild obstructive sleep apnoea, but a multiple sleep latency test was indicative of narcolepsy, with a mean sleep latency of 15 seconds and sleep onset rapid eye movement in all four naps. Fluoxetine has controlled his cataplexy; stimulants for his daytime sleepiness and continuous positive airways pressure at night for his sleep apnoea have made a modest impact.

Case 3—A 41 year old retired social worker was referred from an epilepsy clinic. Fifteen years before she had begun to experience episodes resembling "a waking dream:" something familiar would come into her mind, but she would be unable to recall its content afterwards. Six years before these episodes had become more sustained. She developed the sense that there "was a film running in my head," comprising intrusive mental contents, both images and thoughts. She also experienced occasional feelings of déjà vu. Temporal lobe epilepsy was suspected. Computed tomography of the brain and an electroencephalogram gave normal results; treatment with carbamazepine was ineffective. Two years before we saw her the "film running in the head" had resolved itself into individual pictures that entered her mind for a second or so at a time. She sometimes recognised these from recent dreams, and they tended to have a strong emotional content. They appeared three or four times a day; she

Polysomnography

Polysomnography involves the measurement of several physiological variables during sleep and aids the diagnosis of sleep disorders. The variables most commonly assessed are brain activity and sleep stage, using electroencephalography, muscle activity at several sites including eye movements, using surface electromyography, chest and abdominal movements related to breathing, oral or nasal airflow, heart rate using electrocardiography, and tissue oxygenation using pulse oximetry. The main use of polysomnography in the diagnosis of narcolepsy is to exclude disorders of nocturnal sleep, such as obstructive sleep apnoea, which might explain daytime sleepiness.

had similar experiences on dropping off to sleep, when she felt that "a dream comes straight into my mind." Seven episodes of "waking hallucination" occurred during a 24 hour electroencephalogram recording: during several of these the record showed light sleep with superimposed rapid eye movements. Rapid eye movement also occurred at the onset of overnight sleep. On direct questioning she admitted to daytime sleepiness, with naps at least once a day, but not to cataplexy or sleep paralysis. We believed that her "waking hallucinations" represented a variety of hypnagogic hallucinations, and that these, in combination with daytime sleepiness and sleep onset rapid eye movement, were suggestive of narcolepsy (perhaps not conclusive, however, as some authors require the presence of cataplexy for a definite diagnosis[4]). Her HLA type, determined by polymerase chain reaction amplification with sequence specific primers, was DRB1*15, DRB5*51, DQB1*6, consistent with narcolepsy. A multiple sleep latency test showed a mean sleep latency of 11 minutes, a minimum latency of seven minutes, and two episodes of sleep onset rapid eye movement.

Discussion

Narcolepsy has a prevalence of around 1:2000.[5 6] It can present at any age, most often in the second and third decades of life.[4] A history of excessive daytime sleepiness and cataplexy make the diagnosis extremely likely, but the disorder can present with any combination of excessive daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis. HLA typing reveals the DQB1 0602 subtype in 90% of people with narcoplepsy compared with 12-38% of controls, but the possession of this allele is neither necessary nor sufficient for the disorder.[7] Overnight polysomnography (box) helps to rule out other causes of excessive sleep disorder, such as obstructive sleep apnoea. The multiple sleep latency test (box) generally shows a reduced mean sleep latency and, usually, the occurrence of episodes of sleep onset rapid eye movement.[4]

The phenomenon of narcolepsy can be understood in terms of a dysregulation of rapid eye movement sleep, which is normally associated with dreaming and motor inhibition to prevent the dreams from being acted out.[8] The inappropriate activation of these mechanisms underlies hypnagogic hallucinations, cataplexy, and sleep paralysis. Effective treatment is available.[4] Tricyclic antidepressants and selective serotonin reuptake inhibitors reduce the frequency of attacks of cataplexy, and stimulants including dexamphetamine, methylphenidate, and modafinil reduce the frequency and intensity of sleep attacks.

In cases 1 and 2, diagnostic difficulty stemmed from the misinterpretation of episodes of cataplexy and daytime sleep. Partial recovery of muscle tone, with resulting twitching movements, is common during episodes of cataplexy[4]: this was mistaken for the jerking of a seizure in both cases. Clues to the true nature of these episodes were supplied by both patients having all the symptoms of narcolepsy, their recall for events occurring during their attacks of weakness, and the precipitation of the nocturnal attacks by sexual excitement in case 2. In case 3, the description of elusive reminiscences and déjà vu gave rise to a reasonable suspicion of temporal lobe seizures. However, the patient's own impression that these experiences represented "waking dreams" was born out by investigation.

These cases illustrate the scope for mistaking narcolepsy for epilepsy. The investigation, management, and prognosis of these two conditions are so different that this error should be avoided. Considering the possibility of narcolepsy and inquiring about its four principal symptoms will usually achieve this goal.

The multiple sleep latency test

The multiple sleep latency test, often performed the day after polysomnography, quantifies daytime sleepiness by offering subjects four or five opportunities to fall asleep in a quiet dark room at two hour intervals. The electroencephalogram, eye movements, and muscle tone are monitored. People with narcolepsy typically have a mean sleep latency of less than eight minutes and episodes of rapid eye movement or dreaming sleep within 10 minutes of sleep onset. The sensitivity of a single multiple sleep latency test in narcolepsy has been reported to be 84%[10]; its specificity depends on the care taken to exclude other causes of daytime sleepiness on clinical grounds and using polysomnography.

Narcolepsy and driving

Patients with narcolepsy run a substantially increased risk of falling asleep while driving, with resulting accidents.[9] Patients should report the diagnosis of narcolepsy to the Driver and Vehicle Licensing Agency. Driving will then be permitted "when satisactory control of symptoms is achieved." This is currently a matter for clinical judgment. If a patient continues to drive against medical advice it is a doctor's duty to consider informing the Driver and Vehicle Licensing Agency directly. Research is needed to establish whether computerised tests of vigilance are useful predictors of safety at the wheel in people with narcolepsy.

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Science commentary

Science commentary: HLA typing

Human leucocyte antigens (HLAs) are cell surface molecules found on all nucleated cells. Each individual has a unique set of these antigens, half inherited from each parent, and their typing becomes important before organ transplantation. Typing is also used to identify markers for specific diseases, such as HLA B27, which is known to be closely associated with conditions such as ankylosing spondylitis.

Two main classes of HLA antigens are recognised: HLA class I and HLA class II. HLA class I antigens (A, B, and C in humans) render each cell recognisable as "self," whereas HLA class II antigens (DR, DP, and DQ in humans) stimulate the immune system.[1] Both have been implicated in the rejection of transplanted organs.

Three main processes are used to perform HLA typing. The first is the more conventional serological cytotoxicity method where tiny samples of lymphocytes (taken from from blood or spleen) are added to Terasaki plates. These plates hold individual wells that contain different specific antibodies (from either maternal sera or manufactured monoclonal antibodies). The best cells for class II typing are B lymphocytes, and class I typing can be performed with the remaining leucocytes. Magnetic beads are used to purify the required cells from blood or spleen.

If the HLA antigen and specific antibody bind, and complement is added, the cells in that well will be killed. The pattern of wells showing this cell death allows the deduction of which combination of HLA antigens were present on the original tissue cells.

Another potential method used for HLA typing is flow cytometry, particularly when looking for specific alleles. Here fresh nucleated leucocytes are added to monoclonal antibodies that are labelled with a molecule that fluoresces. Cells with surface antigens that bind to the antibody become fluorescent. The flow cytometer detects the fluorescent cells by detecting the light emitted from them as they pass through a laser beam. Flow cytometry takes about 30 minutes to complete—the time taken to prepare the cells and then run the machine.

A third process is gaining favour where very detailed typing is required—for example, for precise matching in bone marrow transplantation. This process involves extracting the DNA from cells and amplifying the genes that encode for the HLA peptides using polymerase chain reaction techniques. The genes may be matched with known HLA nucleotide sequences found stored in several gene bank databases, including the IMGT/HLA database.

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Progress

After many years at sea as a cruise ship doctor, I am often asked: "How do you keep up to date?" Practising medicine in isolation from other doctors, we may be regarded by our peers as out of touch.

Not at all. We see a frequently changing population of well over 1000 passengers, mainly elderly and most taking at least one prescription medication. So we are in a unique position to observe the medicine currently practised ashore, and this gives us a good insight into "progress." Our therapeutic armamentarium is limited to the more tried and tested generic drugs of proven efficacy.

I doubt that any two people on board are taking exactly the same medication, although I am sure that many medical conditions are similar. It is not uncommon to find patients, especially from the United States, taking a dozen or more different drugs prescribed by different specialists, often without reference to what others have already prescribed. Despite this the patients thrive.

Generic prescribing is sadly becoming increasingly rare and I am sure that, for instance, a lot of normotension is expensively treated with state of the art branded products as a result of peer or patient pressure. Zithromax "Z-Pak" (azithromycin) has replaced Biaxin (clarithromycin), and before that Cipro (ciprofloxacin) as the fashionable antibiotic that American travellers carry to self-medicate for various conditions. And still we see just about every antiemetic apart from our preferred drug of choice (promethazine) prescribed to prevent motion sickness. When scopolamine patches were popular (indeed, for a time, de rigueur) we treated far more passengers for the many and varied side effects of this drug—which is ineffective for seasickness anyway—than we ever saw suffering from motion sickness, which is rare nowadays given the size and stability of modern passenger ships.

What progress have I observed? In nearly a quarter of a century at sea there are only four great therapeutic advances that spring to my mind. Firstly, the advent of cimetidine has greatly reduced the frequency of gastrointestinal haemorrhage, that worst of maritime medical disasters on account of the difficulties involved in blood transfusion at sea. Then, aciclovir, in its various forms, makes treatment of genital herpes, chickenpox, and shingles possible. Streptokinase is of proven value and in our unique situation we are able to administer it within minutes. Lastly, and in my view most importantly, is the use of intramuscular non-steroidal anti-inflammatory drugs to rapidly alleviate the fever and associated symptoms of acute viral illnesses.

With the global increase of seasonal pyrexial flu-like viral illnesses and viral gastroenteritis, we occasionally have outbreaks on board and we see a lot of acutely ill, febrile, elderly people. I learned of the use of non-steroidals anecdotally from a colleague several years ago and I never cease to wonder at their efficacy. As far as I am aware this usage is not documented and no trials have been performed. I am convinced that a lot of seasonal suffering and morbidity could be alleviated if this treatment were trialled and promulgated. When I describe this apparently miraculous treatment to colleagues ashore they look at me as if I have come from the moon, not the ocean deep. Progress?

Andrew Iddles *senior ship's doctor*

We welcome articles of up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to.